Abstract 6407
Spatial remodeling of the immune tumor microenvironment after radiotherapy and CXCL12 inhibition in glioblastoma in the phase 1/2 GLORIA trial

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Background
Radiotherapy (RT) causes upregulation of CXCL12, a chemokine facilitating recruitment of tumor-associated macrophage (TAM) precursors promoting neovasculogenesis and the formation of an immunosuppressive tumor microenvironment (TME). Here, we report an in-depth analysis of the immune TME (iTME) in patients of the multicentric phase 1/2 GLORIA trial (NCT04121455) which combines RT and CXCL12 inhibition with the RNA–Spiegelmer NOX–A12.

Methods
We analyzed tumor tissue of 10 GLORIA patients with newly diagnosed, incompletely resected (n=8) or biopsied (n=2) GBM with ECOG ≤ 2 lacking MGMT promoter methylation. All patients received standard RT and escalating dose levels of continuous (24/7) i.v. infusions of NOX–A12. Two patients underwent re–surgery, whereas one was diagnosed with pseudoprogression (PsP) and one with recurrence. To characterize the iTME, we used highly multiplexed immunofluorescence (mIF) imaging. As a comparison to the GLORIA cohort, we investigated the pre/post-therapeutic iTME of reference patients receiving standard-of-care (n=7) treatment.

Results
In all samples analyzed, CXCL12 co–localized with endothelial cells. Unlike in the reference cohort, matched pre-/post–treatment tissue analysis of the patient with PsP revealed endothelial and gliomal CXCL12 depletion following treatment with NOX–A12, confirming the mode of action of the drug. Both post–treatment GLORIA samples showed intralesional clustering of activated CD8⁺ T cells. In the non-responder diagnosed with recurrence, a pro–tumorigenic spatial rearrangement of the iTME was observed, characterized by a presence of M2–like TAMs in the proximity of the perivascular T cell clusters, confirmed by nearest neighbor analysis. None of the reference patients showed similar alterations of the iTME.
Conclusions

mIF of matched pre-/post-therapy tissue samples from the ongoing GLORIA trial supports the proposed modes of action of RT and NOX-A12 counteracting vasculogenesis and modulating the iTME reflected through its spatial rearrangement. This opens up the question of a targetable, compartment-specific role of CXCL12 to be further assessed.

Clinical trial identification
NCT04121455

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